Immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in Vietnamese healthcare workers

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ABSTRACT

We studied the immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in 554 Vietnamese healthcare workers who were naïve to SARS-CoV-2 infection. Neutralizing antibodies increased after each dose. The sero-conversion rate reached 98.1% after dose 2. Btu at month 3, neutralizing antibodies decreased. The requirement for a third dose warrants further research.

Vaccination is critical to bring COVID-19 under control. Although a vaccine must fulfill the required efficacy criteria in order to receive an approval for use in humans, the rapid development and deployment of COVID-19 vaccines worldwide necessitate follow up studies to better understand the development and persistence of vaccine-induced immunity in different populations. Such knowledge is critical to inform the global vaccination strategies and the development of next-generation vaccines.

Vietnamese people remains relatively naïve to SARS-CoV-2 infections [1, 2]; as of 5th July 2021, 19,579 PCR confirmed cases have been reported in a population of >97 million. Therefore Vietnam is an ideal setting for vaccine evaluation study as the results naturally reflect the immunity induced by COVID-19 vaccines. There has been no report about the immunogenicity of the Oxford-AstraZeneca COVID-19 vaccine from Southeast Asia. We studied the immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in a cohort of 554 healthcare workers of an infectious diseases hospital in southern Vietnam.

METHODS

Setting

The present study was conducted at the Hospital for Tropical Diseases (HTD) in HCMC. HTD is a 660-bed tertiary referral hospital for patients with infectious diseases (including COVID-19) in southern Vietnam [3]. According to the MOH criteria (Supplementary Materials), HTD members of staff were eligible for vaccination and were the first in Vietnam to receive a COVID-19 vaccine in March 2021.

Data collection

We collected demographics and 3ml of blood from the study participants. Blood sampling was scheduled for 7 time points, including before each dose, 14 days after each dose, and

month 1, 3, 6 and 12 after vaccination. After day 28 of the first dose, blood sampling was narrowed down to a subgroup of 144 individuals randomly selected from the study participants for subsequent follow up. The present report focused on the period from baseline to month 3 after the first dose.

Neutralizing antibody measurement

Neutralizing antibodies were measured using an FDA EUA approved assay, namely SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) (GenScript, USA) [4], following to the manufacturer's instructions (Supplementary Materials).

We also included neutralizing antibody data from 11 Vietnamese individuals with asymptomatic or mild SARS-CoV-2 infection for comparative analysis (Supplementary Materials) [5].

Statistical analysis

We used Fisher exact, χ^2 or Mann-Whitney U test to compare between groups (when appropriate). Logistic regression was used to assess association between the probability of having detectable neutralizing antibodies and age. Linear regression was used to assess the association between neutralizing antibodies levels and age. The analyses were carried using Prism 9.0.2 (graphpad.com).

Ethics

The study was approved by the Institutional Review Board of HTD and the Oxford Tropical Research Ethics Committee, University of Oxford, UK. Written informed consents were obtained all the participants.

RESULTS

Demographics of the study participants

A total 649/894 (73%) HTD staff consented to participate in the vaccine evaluation study. 554/649 (85%) participants were successfully followed-up up to day 28 after the first dose and were thus included for analysis as whole group. The 554 study participants aged between 24 and 65 years (median: 37 years). Females were predominant (Supplementary Table 1)

Of the 144 participants of the subgroup, 104 (72%) and 95 (66%) were successfully followed-up up to 14 after the second dose and month 3 after the first dose, respectively. The age and gender distributions of these subgroups were comparable with that of the whole group (Supplementary Table 1). The window time between the first and the second dose was six weeks.

Development of detectable neutralizing antibodies

Because HTD members of staff were naïve to SARS-CoV-2 infection [1], we first focused our neutralizing antibody measurement on the baseline samples collected before the first dose of the subgroup. At baseline, none of the study participants had detectable neutralizing antibodies (Supplementary Table 2). At day 14 and 28 after the first dose, the proportions of the study participants with detectable neutralizing antibodies increased from 27.3% (151/554) to 78.0% (432/554), respectively among all 554 individuals of the whole group. The proportion of the study participants with detectable neutralizing antibodies reached 98.1% (102/104) at 14 days after the second dose, and then slightly dropped to 94.7% (90/95) at month 3 after the first dose (i.e. six weeks after the second dose) (Supplementary Table 2).

Kinetics of neutralizing antibody levels

Neutralizing antibody levels measured at day 28 after the first dose were significantly higher than that measured at day 14 (Figure 1A), but comparable with that measured at 6 weeks (Figure 1B). At day 14 after the second dose, neutralizing antibodies significantly increased, and were comparable with that obtained from Vietnamese people with asymptomatic or mild infection (Figure 1B). At month 3 after the first does neutralizing antibody levels were significantly lower than that measured at 14 days after the second dose (Figure 1B)

Neutralizing antibodies vs. age and gender

At day 14 after the first dose, the development and levels of detectable neutralizing antibodies among 554 study participants were negatively correlated with age. This difference was less profound at day 28, especially with regard to the development of detectable neutralizing antibodies (Figure 1C&D). At these corresponding time points, similar trends were also observed among individuals of the subgroup, but the difference was not significant (Supplementary Figure 1&2), likely because of the small sample size. At 14 days after the second dose and month 3 after the first dose, the proportion of individuals with detectable neutralizing antibodies was similar across age groups (Supplementary Figure 1B&C).

With the exception of day 28 after the first dose, neutralizing antibody levels and the proportion of study participants with detectable neutralizing antibodies were comparable between males and females (Supplementary Table 2 and Supplementary Figure 3).

DISCUSSION

We report the immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in a cohort of 554 Vietnamese healthcare workers who were naïve to SARS-CoV-2 infection. We showed that Oxford-AstraZeneca COVID-19 vaccine is immunogenic. At month 3 after the first dose, neutralizing antibody levels reduced significantly, while the seroconversion rate slightly declined from 98.1% at day 14 after the second dose to 94.7%.

Findings from the original phase 2/3 trial showed that spike protein specific IgG developed within two weeks after vaccination, and at 14 days after the second dose its titers increased with a seroconversion rate of 208/209 (>99%) [6]. Consistently, our study showed the development and the levels of neutralizing antibodies significantly increases after each dose, with the former reaching 98% at 14 days after the second dose. Parallel with these reports are real-word data from the UK showing that the administration of the second dose increased protection against SARS-CoV-2 infection from 65% by dose 1 to 70% by dose 2 among vaccine recipients [7]. A single dose of Oxford-AstraZeneca or Pfizer COVID-19 vaccines reduced COVID-19 hospital admissions among vaccine recipients by 88% and 91%, respectively in Scotland [8].

Older individuals, especially those 80 years or above, without prior infection had lower levels of neutralizing antibodies induced by the first dose than younger adults [9, 10]. These age-dependent responses were most profound within the first 3 weeks after vaccination, but were resolved by the administration of the second dose [9]. Although similar trends were observed in our study, at day 28 after the first dose, the differences in our study were negligible, especially in terms of the seroconversion rate. None of our study participant was older than 71 years, explaining why the observed differences were less profound as compared to the UK population based study.

The results provide reassuring evidence for the effectiveness of the proposed vaccination strategy aiming at prioritizing the first dose for as many people as possible in the first instance [11]. However, our results also emphasize the importance of the second dose, especially in older people, while it remains unknown whether the third dose is needed to provide long-term protection. A decline in antibody titers was recorded at week 8-12 after the first two doses among 75 study participants in the UK [12]. But the administration of the third dose helped boost the immune response. Antibody waning is presumably more profound among individuals without prior infection. Follow study is therefore critical to assess the levels of antibody waning among our study participants.

Our study has some limitations. We did not study cellular immunity, especially T cell response. And due to the age and gender structure in nature of HTD staff, we did not include participants older than 71 years and females were predominant among our study subjects. Compared with males, females seemed to better respond to Oxford-AstraZeneca COVID-19 vaccine at day 28 after the first dose, which warrants further research.

CONCLUSIONS

Oxford-AstraZeneca COVID-19 vaccine is immunogenic in Vietnamese healthcare workers who were naïve to SARS-CoV-2 infection. Neutralizing antibody levels decreased at month 3 after vaccination. The requirement for a third dose warrants further research. These data are critical to informing the deployment of COVID-19 vaccine in Vietnam and other Southeast Asian countries.

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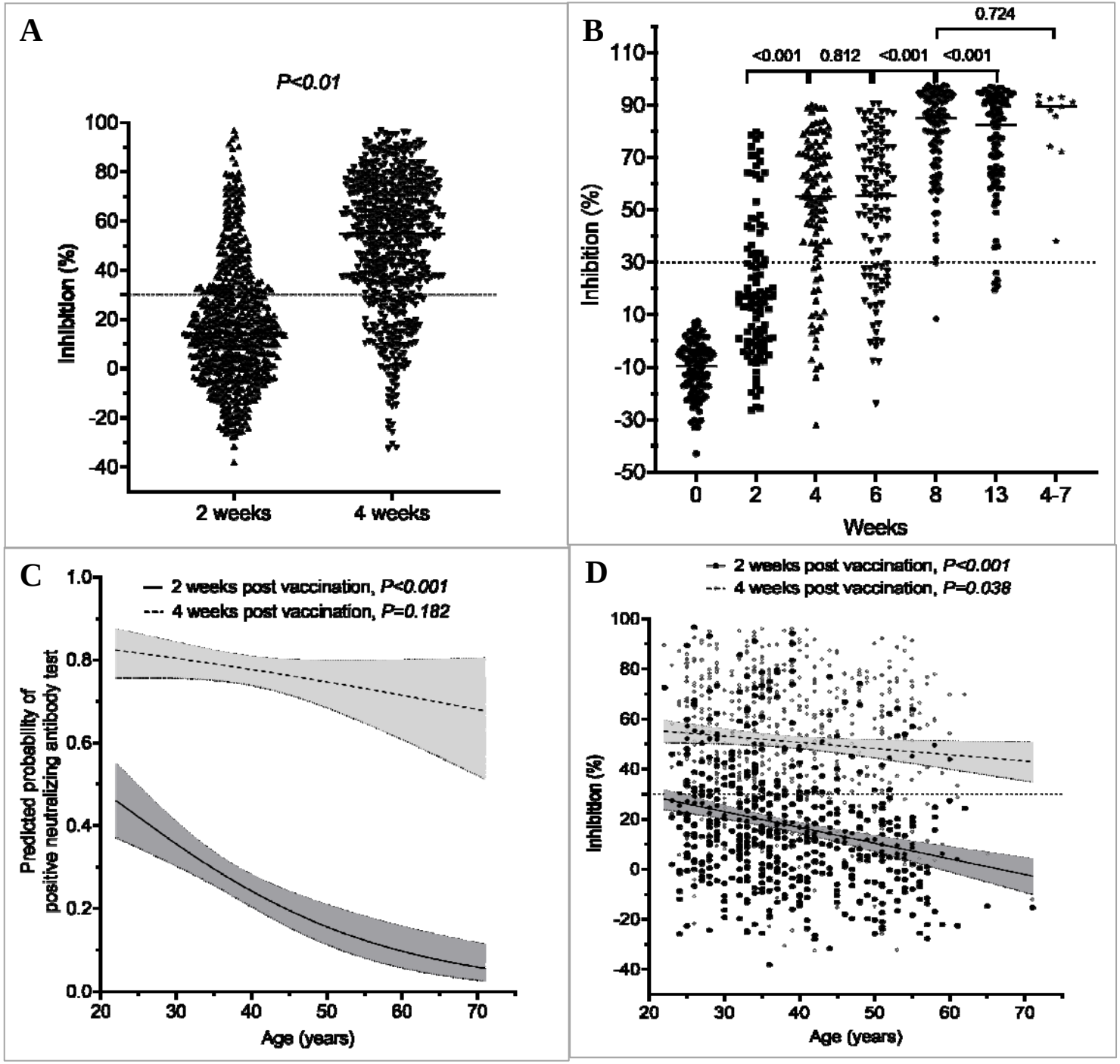
LEGENDS TO FIGURES

Figure 1: Development of neutralizing antibodies levels and their associations with age; **A**) Neutralizing antibody levels measured at 14 and 28 days after the first dose of 554 study participants; **B**) Neutralizing antibody levels measured at time points from baseline to month 3 after the firs dose of the subgroups; **C**) Association between age and the probabilities of having detectable neutralizing antibodies at 14 and 28 days after the first does of 554 study participants; **D)** Association between age and neutralizing antibody levels measured at 14 and 28 days after the first dose of 554 study participants

Notes to figure 1B: Data on neutralizing antibody levels obtained from 11 convalescent sera collected at week 4-7 (last column) from cases with mild or asymptomatic infection was included as references. Black circles: data for 2 week time point and grey circles: data for 4 week time point

Figure 1



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COVID-19 vaccine rollout in Vietnam

Vietnam received the first 117,000 doses of Oxford-AstraZeneca COVID-19 vaccine in early March 2021. High-risk groups, especially frontline healthcare workers, were prioritized for vaccination. The window time between two doses was set for 4 weeks, with some variation depending on the availability of the vaccine.

List of groups prioritized for COVID-19 vaccination in Vietnam

1. Frontline healthcare workers of COVID-19, including people whose work is to deal with COVID-19 prevention and control work (members of COVID-19 steering committees at all levels, staff at state-run quarantine sites, people conducting contract tracing and epidemiological investigations, volunteers, reporters among others), military and public security forces
2. Vietnamese diplomats, customs and immigration officers
3. Essential service workers in sectors such as aviation, transport, tourism, electricity and water supply
4. Teachers and individuals working at education and training facilities, and those working at State agencies with regular contact with various people
5. People with chronic diseases or aging above 65
6. Residents in outbreak hotspots in Vietnam
7. Poor people, Policy beneficiaries
8. Those who will be sent abroad for learning and working
9. Other people determined by the Ministry of Health

Measurements of neutralizing antibody using Surrogate virus neutralization assay

Surrogate virus neutralization assay (sVNT) is an assay that measures spike protein receptor binding domain (RBD)-targeting neutralizing antibodies (RBD-targeting NAbs) Prior to testing, plasma samples were first diluted 1:10 and then inactivated at 56^0C for 30 minutes. The experiments were carried out according the manufacturer's instruction. The obtained results were expressed as percentage of inhibition with the 30% cut-off applied. The percentage of inhibition measured by sVNT has been shown to well correlate with the neutralizing antibody tiers measured by the conventional plaque reduction neutralization assay [1].

Neutralizing antibody data from cases of natural infection

To compare the development of neutralizing antibodies induced by vaccination against that of natural infection, we included data from 11 Vietnamese patients who had mild or asymptomatic infections. Details about these individuals and neutralizing antibody measurement were detailed in our recent report [2].

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2. Mai, H.K., et al., *Long-Term Humoral Immune Response in Persons with Asymptomatic or Mild SARS-CoV-2 Infection, Vietnam.* Emerg Infect Dis, 2021. **27**(2): p. 663-666.

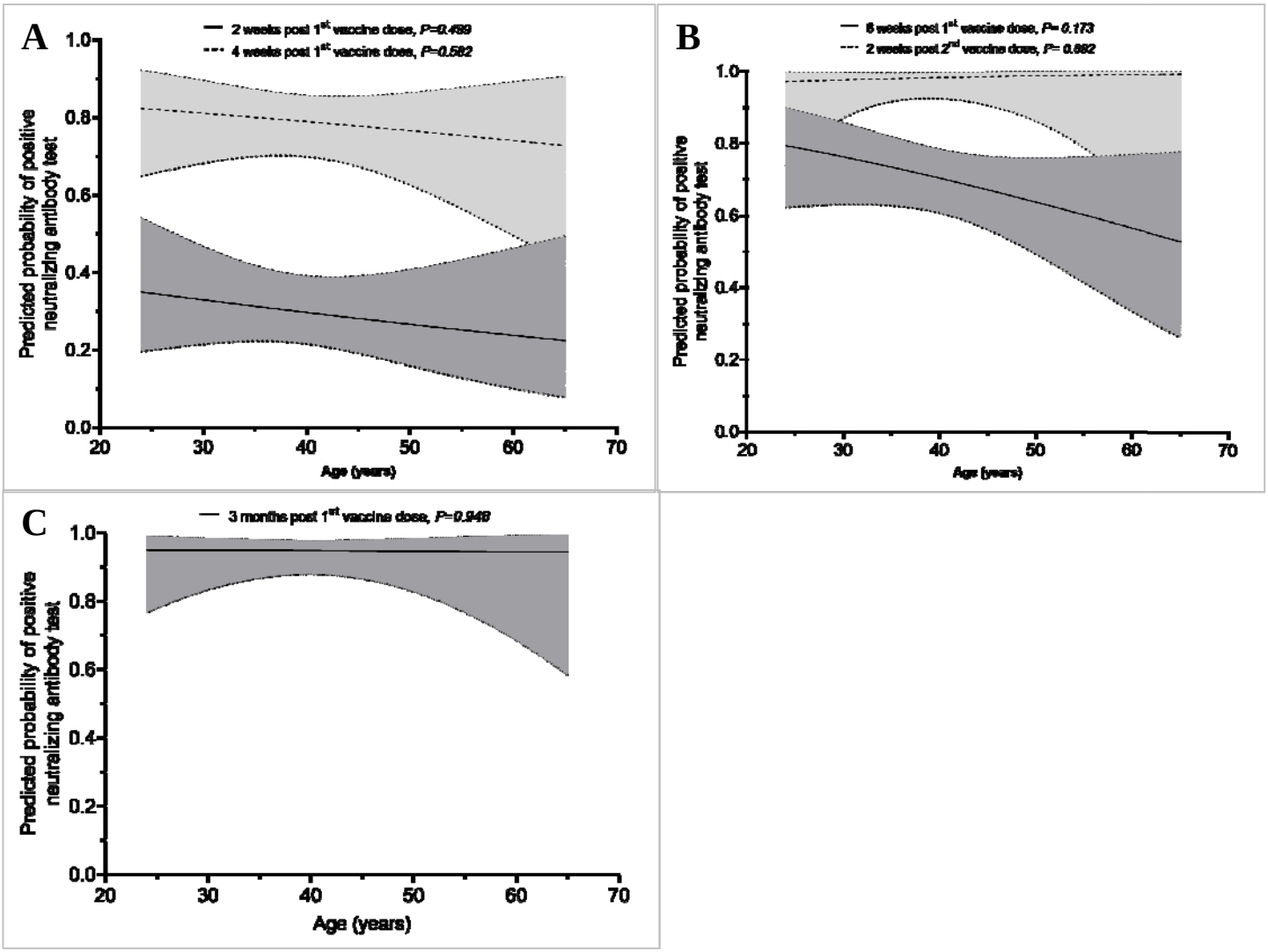
Supplementary Table 1: Demographics of the study participants

	Whole group (N=554)	**Subgroup (N=104)**	**Subgroup (N=95)**
Male, n (%)	136 (25)	25 (24)	21 (22)
Female, n (%)	418 (75)	79 (76)	73 (78)
Median age in years (range)	36 (22 – 71)	37 (24 – 65)	37 (24-65)
Age groups			
20-39, n (%)	332 (60)	57 (55)	50 (53)
40-60, n (%)	217 (39)	46 (44)	43 (46)
61-71, n (%)	5 (1)	1 (1)	1 (1)

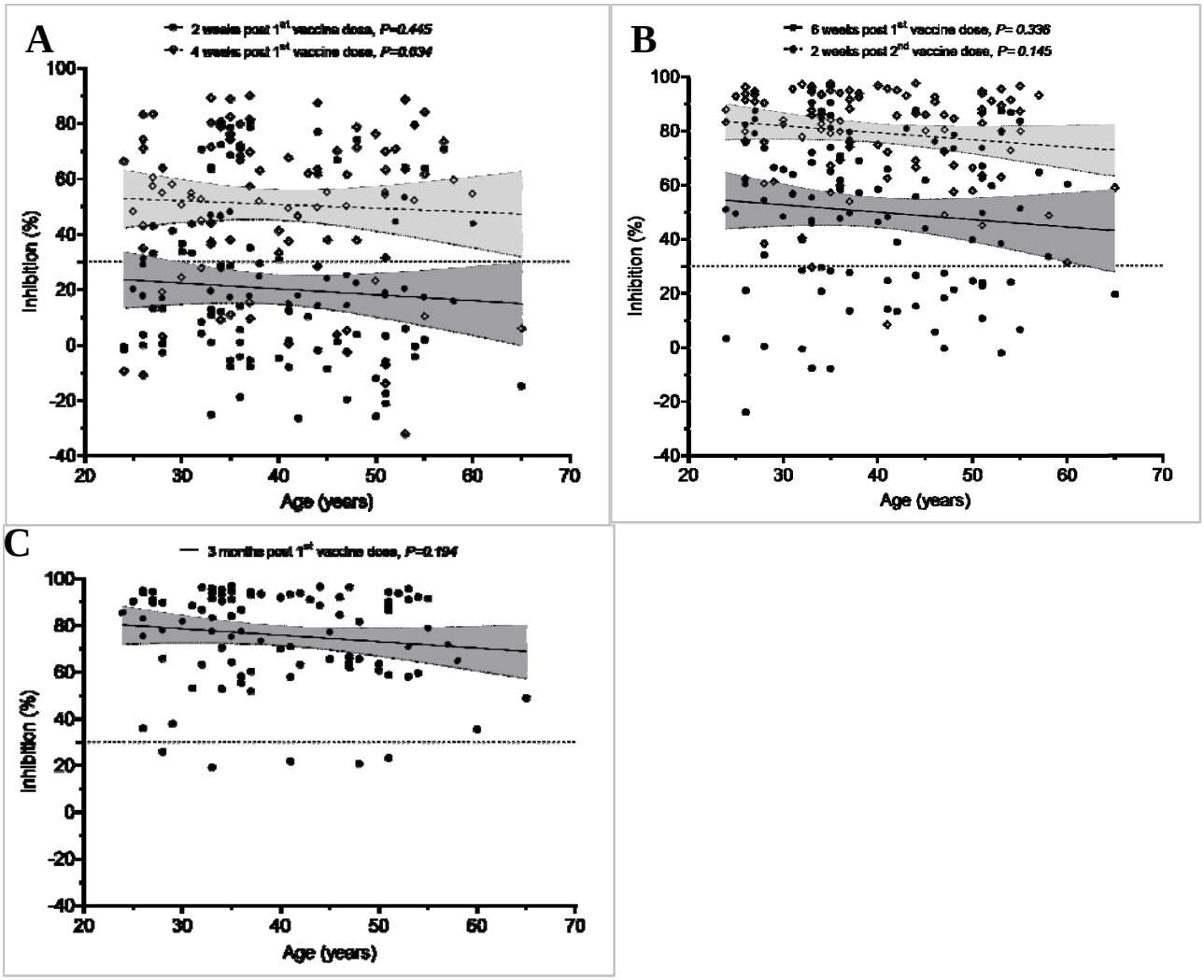
Supplementary Table 2: The proportion of study participants with detectable neutralizing antibodies after vaccination

Time point	Whole group				Subgroup			
	Total (N=554)	Male (N=136)	Female (N=418)	P value*	Total (N=104)	Male (N=25)	Female (N=79)	P value*
Baseline, n (%)	0	0	0	NA	0	0	0	NA
14 days after dose 1, n (%)	151 (27.3)	40 (29.4)	111 (26.6)	0.52	31 (29.8)	10 (40.0)	21 (26.6)	0.20
28 days after dose 1, n (%)	432 (78.0)	97 (71.3)	335 (80.1)	0.031	82 (78.8)	20 (80.0)	62 (78.5)	0.87
Before dose 2, n (%)	N/A	N/A	N/A	N/A	73 (70.2)	17 (68.0)	56 (70.1)	0.78
14 days after dose 2, n (%)	N/A	N/A	N/A	N/A	102 (98.1)	24 (96.0)	78 (98.7)	0.43
Month 3 after the first dose**	NA	NA	NA	NA	89 (94.7)	68 (95.5)	21 (95.5)	1

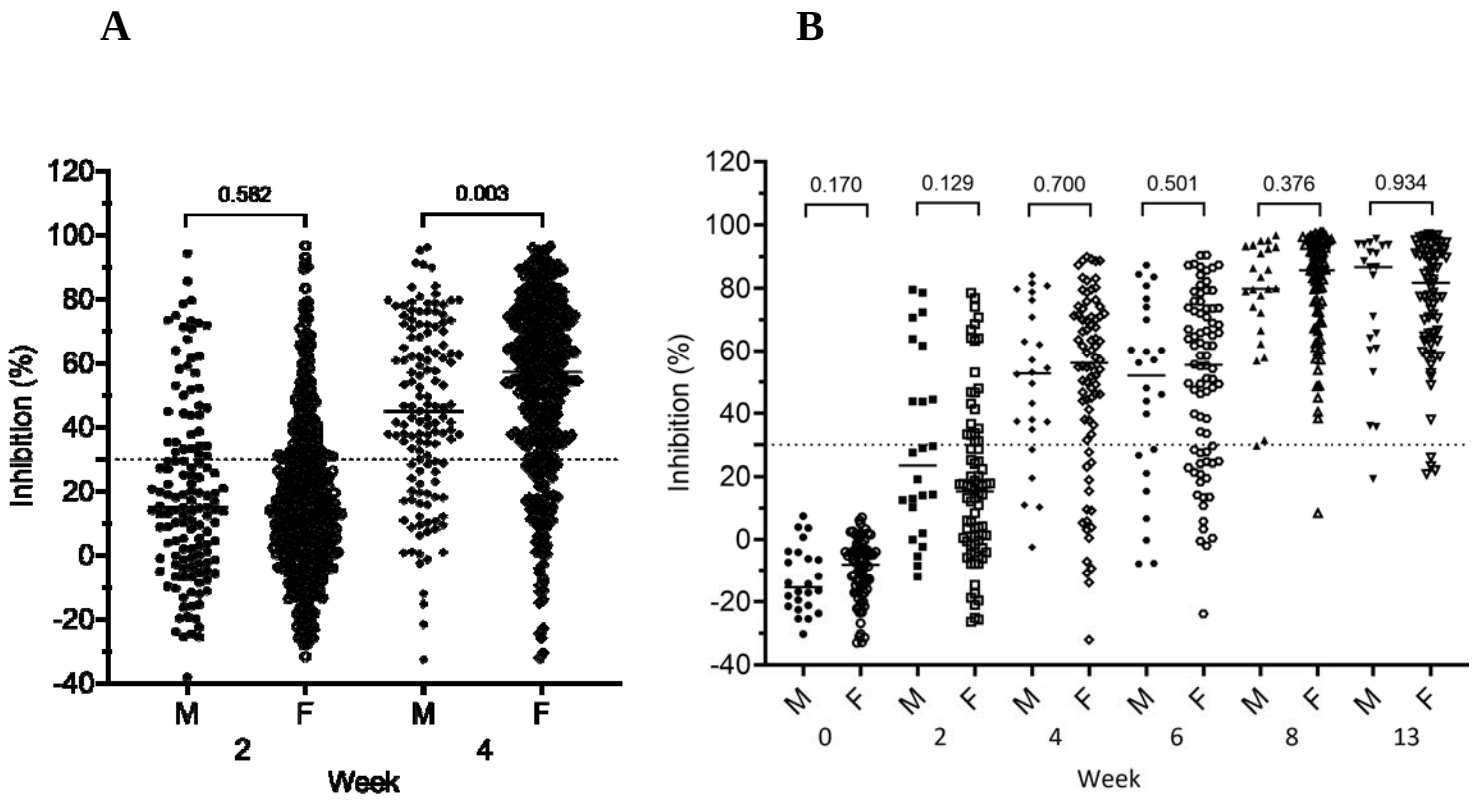
Notes to Supplementary Table 2: *for comparison between males and females, NA: non-applicable, ** n=95 (male: 22 and females: 72)



Supplementary Figure 1: Probability of having detectable neutralizing antibodies among the study participants selected for assessment of the impact of the second dose. **A**) At 2 and 4 weeks after the first dose (n=104), **B**) Before the second dose (i.e.6 weeks after the first dose) and 2 weeks after the second dose (n=104) and **C**) at month 3 after the first dose (n=95)



Supplementary Figure 2: Neutralizing antibody levels of participants selected for assessment of the impact of the second dose. **A**) At 2 and 4 weeks after the first dose (n=104), **B**) Before the second dose (i.e.6 weeks after the first dose) and 2 weeks after the second dose (n=104) and **C**) at month 3 after the first dose (n=95)



Supplementary Figure 3: Association between neutralizing antibody levels and gender. **A**) At 2 and 4 weeks after the first dose of the whole group (n=554), **B**) From baseline to month three after the first dose of the subgroup